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Insights into the protective effects of influenza vaccination: More hospitalizations but lower follow-up mortality during the 2014/15 influenza season in a Swiss cohort

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Abstract: **BACKGROUND:** Observational studies of influenza vaccination are criticized as flawed due to unmeasured confounding. The goal of this cohort study was to explore the value and role of secondary claims data to inform the effectiveness of influenza vaccination, while systematically trying to reduce potential bias. **METHODS:** We iteratively reviewed the components of the PICO approach to refine study design. We analyzed Swiss mandatory health insurance claims of adult patients with chronic diseases, for whom influenza vaccination was recommended in 2014. Analyzed outcomes were all-cause mortality, hospitalization with a respiratory infection or its potential complication, and all-cause mortality after such hospitalization, adjusting for clinical and health care use variables. Cox and multi-state models were applied for time-to-event analysis. **RESULTS:** Of 343,505 included persons, 22.4% were vaccinated. Vaccinated patients were on average older, had more morbidities, higher health care expenditures, and had been more frequently hospitalized. In non-adjusted models, vaccination was associated with increased risk of events. Adding covariates decreased the hazard ratio (HR) both for mortality and hospitalizations. In the full model, the HR [95% confidence interval] for mortality during season was 0.82 [0.77-0.88], and closer to null effect after season. In contrast, HR for hospitalizations was increased during season to 1.28 [1.15-1.42], with estimates closer to null effect after season. HR in multi-state models were similar to those in the single-outcome models, with HR of mortality after hospitalization negative both during and after season. **CONCLUSION:** In patients with chronic diseases, influenza vaccination was associated with more frequent specific hospitalizations, but decreased risk of mortality overall and after such hospitalization. Our approach of iteratively considering PICO elements helped to consider various sources of bias in the study sequentially. The selection of appropriate, specific outcomes makes the link between intervention and outcome more plausible and can reduce the impact of confounding.

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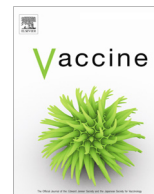


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Insights into the protective effects of influenza vaccination: More hospitalizations but lower follow-up mortality during the 2014/15 influenza season in a Swiss cohort



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ABSTRACT

Background: Observational studies of influenza vaccination are criticized as flawed due to unmeasured confounding. The goal of this cohort study was to explore the value and role of secondary claims data to inform the effectiveness of influenza vaccination, while systematically trying to reduce potential bias. **Methods:** We iteratively reviewed the components of the PICO approach to refine study design. We analyzed Swiss mandatory health insurance claims of adult patients with chronic diseases, for whom influenza vaccination was recommended in 2014. Analyzed outcomes were all-cause mortality, hospitalization with a respiratory infection or its potential complication, and all-cause mortality after such hospitalization, adjusting for clinical and health care use variables. Cox and multi-state models were applied for time-to-event analysis.

Results: Of 343,505 included persons, 22.4% were vaccinated. Vaccinated patients were on average older, had more morbidities, higher health care expenditures, and had been more frequently hospitalized. In non-adjusted models, vaccination was associated with increased risk of events. Adding covariates decreased the hazard ratio (HR) both for mortality and hospitalizations. In the full model, the HR [95% confidence interval] for mortality during season was 0.82 [0.77–0.88], and closer to null effect after season. In contrast, HR for hospitalizations was increased during season to 1.28 [1.15–1.42], with estimates closer to null effect after season. HR in multi-state models were similar to those in the single-outcome models, with HR of mortality after hospitalization negative both during and after season.

Conclusion: In patients with chronic diseases, influenza vaccination was associated with more frequent specific hospitalizations, but decreased risk of mortality overall and after such hospitalization. Our approach of iteratively considering PICO elements helped to consider various sources of bias in the study sequentially. The selection of appropriate, specific outcomes makes the link between intervention and outcome more plausible and can reduce the impact of confounding.

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1. Introduction

Vaccination is known to prevent influenza infections [1,2], and some studies argue that it also attenuates their course and reduces the need for intensive care treatment [3–5], prevents cardiovascular events [6,7] and respiratory complications [8]. However, the magnitude of the total effect on subsequent health outcomes, hospitalizations, mortality, and thus the overall impact on health is

Abbreviations: RCT, randomized controlled trial; PCG, pharmaceutical costs groups; FOPH, the Swiss Federal Office of Public Health; SwissDRG, Swiss Diagnosis-Related Groups; SHS, Swiss Health Survey; ECDC, the European Centre for Disease Prevention and Control; HR, hazard ratio; CI, confidence interval.

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debated, especially in older persons [9,10]. High-quality evidence is lacking, particularly for outcomes such as mortality, because randomized controlled trials (RCTs) are ethically questionable in the populations of greatest interest [11]. It is argued that a genuine uncertainty over the effect of the vaccination on mortality is not present, and vaccination is already broadly recommended for personal and public health as part of standard care [12,13].

However, current ambiguity on the real-world effects of vaccination potentially undermines its uptake and could even contribute to vaccination coverage being low in many countries worldwide [14–16]. Without precise quantification of the expected effect, the potential benefit of vaccination-related public campaigns and policies is also ambiguous.

1.1. Observational studies with administrative data

The lack of real-world RCTs makes observational studies based on secondary data the next logical step. However, observational, especially cohort, studies are sometimes criticized as systematically flawed due to unmeasured confounding [17–19]. The inability to completely rule out inherent biases, particularly when unspecific outcomes are studied, has resulted in some recommendations to avoid such studies altogether or to focus on test-negative design [18,20].

Nevertheless, observational studies of secondary administrative data can potentially contribute valuable information. Finding a suitable application for them is especially attractive as such data are readily available and could cover the whole population nationally or regionally. With appropriate planning (study design) and analysis strategy, observational studies can yield meaningful estimates of effect size and inform the research questions of future RCTs and other studies. Also, they could address outcomes that are unfeasible to investigate with an RCT due to low event rates.

1.2. Research question and aims of the study

The goal of this study was to explore the value and role of secondary claims data to inform the effectiveness of influenza vaccination in a systematic manner, thereby addressing recent methodological debates. We aimed to achieve sufficient reduction of threats to validity by carefully developing the study design according to the basic elements of the PICO approach: the selection of population, intervention, comparator group (control of confounding), and outcomes.

We compared the effect of vaccination on several health outcomes of varying specificity for influenza (all-cause mortality, specific hospitalizations with a respiratory infection or its potential

complication, and mortality after such hospitalizations). We were the most interested in the attenuating effect of vaccination on subsequent outcomes after an infection, such as mortality after influenza-related hospitalization.

2. Methods

2.1. Study framework and research question

We explored how our broad research question could be specified and answered with administrative claims data and the potential biases reduced, by iteratively reviewing the components of the PICO approach and refining study design (Fig. 1) [21,22]. PICO approach is primarily used to formulate clinical questions [21], but can also be employed as a strategy to focus a research question.

First, we considered the *population* – adult patients with chronic diseases for whom The Swiss Federal Office of Public Health (FOPH) recommends vaccination. We additionally analyzed the subgroup of ≥ 65 -years-old persons with chronic diseases (≥ 65 subgroup). We hypothesized that the health status of older persons within this population would be defined better, as more health services are used, and thus, diagnoses are better captured in claims data.

Second, we defined *intervention* as vaccination occurring between September 1 and December 31, 2014. In the models, we included vaccination as a time-varying exposure. Misclassification could not be avoided entirely, as some vaccination paid out-of-pocket may not be captured in the claims data.

Third, to improve *comparability* of the vaccinated and non-vaccinated groups, we controlled for potential confounding and sequentially adjusted for (1) standard variables: age, sex, indicators of major chronic diseases, and number of pharmaceutical costs groups (PCG) in 2014, i.e., specific types of prescribed medications used as markers of chronic conditions [23], (2) additional variables of health care use and expenditure in the previous year (2013). The variables are described in detail in the next section.

Fourth, we modelled all-cause mortality and specific hospitalizations as *outcomes*. We included both outcomes in a multi-state model to account for competing risks and investigate mortality *after* hospitalization. We expected specific hospitalizations and mortality after hospitalization to be more specific outcomes than all-cause mortality.

Based on the refined research question, we formulated these hypotheses: that influenza vaccination would be associated with a smaller risk of mortality, specific hospitalization, and mortality after such hospitalization; that the effect will be greater on specific outcomes than all-cause mortality; and that the effect will be more pronounced *during* than *after* influenza season. We also expected

	Questions considered	Definitions in present study
P Population	Is selected population homogenous enough to expect consistent effect of intervention? Is the effect of confounding consistent in this population? Can confounding be reduced by further restricting the population?	Adult patients with chronic diseases for whom vaccination is recommended by the Swiss Federal Office of Public Health
I Intervention	Is the intervention time-varying? Is misclassification avoided?	Influenza vaccination between September 1 and December 31, 2014, as a time-varying exposure
C Comparison	Are the groups comparable (exchangeable)? Is there sufficient control for health status and other relevant confounders?	Vaccinated and non-vaccinated groups, controlling for: 1) standard variables: age, sex, indicators of major chronic diseases, and number of PCG, 2) additional variables of health care use and expenditure in the previous year: hospitalization for acute disease, stay in a nursing home, and residuals of the total reimbursed health care expenditure in 2013.
O Outcome	Are outcomes specific to the intervention? Can the effect of confounding be reduced by choosing more specific outcome?	All-cause mortality, specific hospitalizations with a respiratory infection or its potential complication, and mortality after specific hospitalization.

Fig. 1. Iterative study improvement framework based on questions related to each element of PICO.

the estimated effect to be more accurate in the ≥ 65 subgroup and after adjusting for additional variables.

2.2. Dataset and population

We analyzed mandatory health insurance claims from the Helsana Group, covering approximately 1.2 million people (15% of the Swiss population). Basic mandatory health insurance in Switzerland is provided by several private companies, Helsana Group being one of the largest.

The Swiss Federal Office of Public Health (FOPH) recommends influenza vaccination for persons with increased risk for influenza complications (such as ≥ 65 -year-old persons, patients with chronic diseases, pregnant women, and premature newborns) and those regularly in contact with such persons or with occupational risk factors [13]. In this study, we included Helsana-insured patients older than 18 years with a clinical indicator of cardiovascular, respiratory, metabolic, neurologic, musculoskeletal, hepatic or renal disease or immune deficiency, as defined by the FOPH recommendations [13], for whom vaccination would be recommended. Indicators of these conditions were relevant PCG in 2014 and hospitalizations with a relevant diagnosis in 2013. Patients with incomplete insurance coverage in years 2014 or 2015, not surviving until September 1, 2014, receiving reimbursement for outpatient services via lump-sums in 2014 (which comprises some patients living in nursing homes), asylum seekers, those living outside Switzerland, and Helsana employees were excluded.

2.3. Exposure (influenza vaccination), outcome and covariates

For included patients, we screened for influenza vaccination claims (coded as J07BB02 with the Anatomical Therapeutic Chemical Classification System (ATC) [24]) between September 1 to December 31, 2014. A person was defined as immunized (effectively vaccinated) after two weeks from the claim.

The beginning of the first specific hospitalization in each period and death were recorded as outcome events. Specific hospitalizations were identified by relevant Swiss Diagnosis-Related Groups codes (SwissDRG, reflecting jointly major inpatient diagnoses and

interventions [25], referred to as *hospitalization* further on), which are detailed in the Supplementary Table 1a. The observation time was divided into three periods: before (September 1 – December 14, 2014), during (December 15, 2014 – May 3, 2015) and after (May 4 – August 31, 2015) the influenza season, based on the European Centre for Disease Prevention and Control (ECDC) report [26]. An illustrative timeline of exposure and outcomes is shown in Fig. 2.

Additional explanatory variables were age, sex, number of PCG in 2014, binary variables of major chronic diseases, and variables of health care use and expenditure in 2013. Variables of major chronic diseases included indicators for cardiovascular, respiratory, metabolic, neurologic, musculoskeletal, hepatic or renal disease or immune deficiency. Binary variables of health care use were: (1) an indicator of any hospitalization for acute disease, and (2) any stay in a nursing home. To reflect health care expenditure, we used the residuals of the total reimbursed expenditure in 2013, after modelling it with the predictive model used for Swiss risk equalization between health insurers [27]. This model uses variables of sex, age, and comorbidities to predict the annual health care expenditure. Thus, a positive residual could be an indicator of poor health status, independent of these variables. As the latter variables were included in the models as covariates separately, residuals instead of the total expenditure were used to prevent multicollinearity.

2.4. Sequence of data analysis

Baseline characteristics for non-vaccinated and vaccinated patients (all and ≥ 65 subgroup) were calculated as percentages for binary and means with standard deviation for continuous variables. Propensity models for vaccination were constructed but eventually not used due to low sensitivity.

Separate Cox models were constructed for mortality and hospitalizations, for all patients and the ≥ 65 subgroup. The effect of vaccination was stratified by time period. In addition, multi-state models including both death and hospitalizations, and thus considering death after hospitalization, were run for all patients and the ≥ 65 subgroup. One expected effect of vaccination was attenuation of influenza infection and thus decreased mortality after

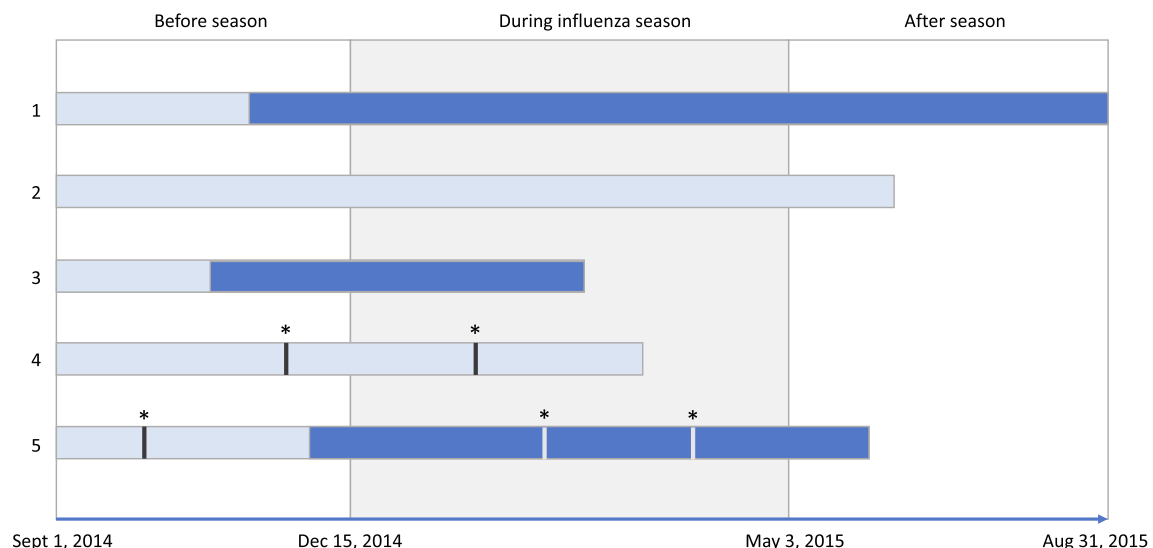


Fig. 2. Observation period, intervention (vaccination) and outcomes timeline. The observation period was between Sept 1, 2014, and Aug 31, 2015. It was divided into three periods: before, during and after influenza season. Lines 1–5 represent example persons in the analyzed population. Dark blue represents vaccinated person-time (1,3,5). Vertical lines with * represent hospitalizations, regarded as events that happen on the hospitalization date. Death within the same time period as a hospitalization is a separate outcome in the multi-state model (4). The observation period ends on August 31, 2015 (1) or death, if earlier (2,3,4,5).

hospitalization. Multi-state models can handle such multiple competing endpoints in a time-to-event analysis, and help to discern their interactions [28]. The analysis was done with R 3.6.0 [29].

The probability of vaccination is not constant through the *before* influenza season. Vaccination utilization is usually low before September, increases until mid-November and then decreases to low again by the end of December. Therefore, the probability of being vaccinated is not proportional to time in the *before* season. Furthermore, the relationship between the risk of mortality and propensity for vaccination might not be constant through the *before* season. In consequence, a person with high mortality risk (i.e., terminally ill) might be disproportionately more likely to be vaccinated if surviving until December, as compared to surviving until October. For these reasons, we assumed that estimates of vaccination effect would not be accurate in the *before* season and analyzed only outcomes in the periods *during* and *after* influenza season.

All procedures performed in the study were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments. Study data were anonymized before analysis. According to the national ethical and legal regulations, ethical approval was not required for this type of retrospective study. This was confirmed by a waiver of the competent ethics committee (Kantonale Ethikkommission Zürich, dated January 11, 2017).

3. Results

Baseline characteristics of the study population are shown in Table 1. Of 343,505 included persons, 22.4% were vaccinated, and 35.0% of 177,107 in the ≥ 65 subgroup. Vaccinated patients were older on average, had more morbidities, higher health care expenditures, and had been more frequently hospitalized for acute disease or stayed in a nursing home in the previous year.

Hazard ratios (HR) for vaccination effect on mortality and hospitalizations during and after influenza season are shown in Table 2. In non-adjusted models, vaccination was associated with increased risks of events. Adjusted HR estimates for all patients and the ≥ 65 subgroup were similar. Adding covariates decreased HR both for mortality (away from null effect) and hospitalizations (closer to null effect). In the full model, the HR [95% CI] for mortality during season was 0.82 [0.77–0.88] for all and 0.82 [0.77–0.88] for the ≥ 65 subgroup. It was closer to null effect after season. In contrast, HR for hospitalizations was greater than 1 during season,

with a wider confidence interval than for the mortality: 1.28 [1.15–1.42] for all and 1.22 [1.09–1.36] for the ≥ 65 subgroup. The estimates after season were closer to null effect, with slightly wider confidence intervals, overlapping HR of 1. Effect estimates of the models are shown in full in Supplementary Table 2a.

HR in multi-state models were similar to those in the single-outcome models (Table 3). HR of mortality after hospitalization was below 1 for all and the ≥ 65 subgroup during and after season, with wide confidence intervals overlapping HR of 1.

In a sensitivity analysis, a wider and a narrower definitions of influenza season were applied, yielding similar estimates and confidence interval bounds of the vaccination effect on mortality, hospitalizations, and mortality after hospitalizations (details in Supplementary Files 1a and 1b).

4. Discussion

In this study, influenza vaccination was associated with lower mortality during as well as after the influenza season. During the influenza season, we observed an increased risk of hospitalizations with a respiratory infection or its potential complication for the vaccinated persons. Despite this seemingly paradoxical effect, multi-state models showed that mortality after such hospitalizations was decreased, hinting at a potentially attenuating effect of vaccination. In other words, although vaccination may not prevent all infections and hospitalizations, influenza seemed to be less frequently fatal in chronically ill persons and those aged 65 years and older, if vaccinated.

The observed vaccination coverage for patients with chronic diseases was lower than estimated in other studies (22.4% in this vs. 30% in a 2014 FOPH survey [30], and 23.4–42.5% for various chronic diseases in the 2012 Swiss Health Survey (SHS) [31]). It was more similar to other studies in the ≥ 65 subgroup (35.0% in this vs. 29% in persons ≥ 65 years in the FOPH survey, and 43.4–52.0% in the SHS). The reasons for low vaccination uptake in Switzerland have been rarely studied in the general population. In a survey of Swiss health care workers, reporting similarly low vaccination rates, the most commonly stated reasons were fear of short-term adverse effects, insufficient evidence of benefits, and fear of restricted right for self-determination [32].

Reduction of mortality risk in vaccinated persons has been frequently seen in other observational cohort studies, with widely ranging effect estimates [18]. We believe that we were able to

Table 1
Baseline characteristics of chronically ill patients with recommended influenza vaccination in 2014.

	All patients		≥ 65 -year-old	
	Non-vaccinated	Vaccinated	Non-vaccinated	Vaccinated
N (%)	266,588 (77.6)	76,917 (22.4)	115,071 (65.0)	62,036 (35.0)
Sex (female) (N (%))	147,894 (55.5)	43,677 (56.8)	67,166 (58.4)	36,010 (58.0)
Age (mean (SD))	60.52 (16.70)	73.59 (12.14)	75.74 (7.41)	78.12 (7.45)
Acute hospitalization(s) in 2013 (N (%))	39,455 (14.8)	16,245 (21.1)	21,256 (18.5)	13,580 (21.9)
Nursing care in 2013 (N (%))	5585 (2.1)	5379 (7.0)	5272 (4.6)	5162 (8.3)
High outpatient med. costs in 2013 (N (%))	13,958 (5.2)	7325 (9.5)	5512 (4.8)	4637 (7.5)
Health care expenditure in 2013 (CHF, mean (SD))	6460.22 (11677.13)	10395.50 (15203.85)	7624.47 (11861.20)	10106.99 (13813.64)
N of PCG (median (IQR))	2.00 [1.00, 4.00]	3.00 [2.00, 5.00]	3.00 [2.00, 4.00]	4.00 [2.00, 5.00]
Specific PCG and inpatient diagnoses in 2014				
Cardiovascular (%)	183,552 (68.9)	66,310 (86.2)	100,164 (87.0)	56,195 (90.6)
Cancer (%)	7497 (2.8)	2864 (3.7)	4060 (3.5)	2264 (3.6)
Diabetes (%)	33,445 (12.5)	14,944 (19.4)	17,408 (15.1)	11,742 (18.9)
Respiratory (%)	82,736 (31.0)	25,551 (33.2)	31,237 (27.1)	19,822 (32.0)
Immune-suppression (%)	75,949 (28.5)	22,497 (29.2)	26,942 (23.4)	16,861 (27.2)
Neurologic (%)	27,424 (10.3)	10,071 (13.1)	11,497 (10.0)	7886 (12.7)
Kidney/liver (%)	4896 (1.8)	2861 (3.7)	3820 (3.3)	2538 (4.1)

High outpatient medication costs in 2013 were defined as >5000 CHF. N – number, SD – standard deviation, med. – medication, CHF – Swiss Franc, PCG – pharmaceutical costs groups, IQR – interquartile range.

Table 2

Hazard ratio estimates for the effect of vaccination on mortality and hospitalization.

Model covariates	Mortality		Hospitalization	
	During season	After season	During season	After season
All patients				
Vaccination only	2.21 [2.07–2.35]	2.27 [2.10–2.44]	2.57 [2.33–2.83]	2.18 [1.90–2.51]
+ standard covariates	0.86 [0.81–0.92]	0.90 [0.83–0.98]	1.30 [1.17–1.44]	1.10 [0.96–1.27]
Full model	0.82 [0.77–0.88]	0.87 [0.80–0.94]	1.28 [1.15–1.42]	1.09 [0.94–1.25]
≥65-year-old				
Vaccination only	1.30 [1.22–1.39]	1.33 [1.23–1.44]	1.64 [1.47–1.83]	1.40 [1.20–1.63]
+ standard covariates	0.86 [0.80–0.92]	0.88 [0.80–0.92]	1.23 [1.10–1.37]	1.04 [0.89–1.22]
Full model	0.82 [0.77–0.88]	0.85 [0.78–0.92]	1.22 [1.09–1.36]	1.03 [0.89–1.21]

* These models are fully specified in supplementary Table 2a. Only the first hospitalization in the specified season is considered. Standard covariates included age, sex, indicators of major chronic diseases, and number of PCG. Full model included the standard covariates as well as indicators of health care use (hospitalization for acute disease, stay in a nursing home) and expenditure in the previous year (residuals of the total reimbursed health care expenditure, as modelled with the current approach for Swiss risk equalization between health insurers).

Table 3

Multi-state models: hazard ratio estimates for the effect of vaccination on hospitalization and death, and the number of observed events.

	During season			After season		
	D	H	H → D	D	H	H → D
HR [95% CI]						
All persons	0.79 [0.74–0.85]	1.25 [1.13–1.39]	0.79 [0.60–1.04]	0.91 [0.84–0.99]	1.13 [0.97–1.31]	0.79 [0.51–1.22]
≥65	0.80 [0.75–0.86]	1.21 [1.08–1.35]	0.86 [0.64–1.15]	0.88 [0.80–0.96]	1.05 [0.90–1.23]	0.65 [0.41–1.05]
N of events						
All persons	3764	1655	255	2662	861	109
≥65	3407	1307	220	2341	659	88

HR – hazard ratio, CI – confidence interval, N – number, D – death, H – first hospitalization, H → D – death after hospitalization during specified period, all persons – all persons with chronic diseases, included in the study, ≥65 – 65-year-old or older.

Multi-state models consider multiple competing outcomes (hospitalization and death) in the same model. Time periods of during and after season were modelled separately. CI of HR in grey overlap 1.00. Patients that were hospitalized in a previous time period but died in the next one were denoted as H in the previous and as D in the next time period (not H → D), because partitioning of time periods creates an extra time interval between these events.

control for further confounders of health status than most studies by considering additional proxies for it: health care use and expenditure variables. Few observational studies of influenza vaccine effectiveness have adjusted for these variables before. For example, Bellino et al. [33] found that health care expenditure was higher in vaccinated patients, and had a significant effect in Poisson regression models of mortality and hospitalization. In our study, although health care use and expenditure variables had a significant effect in the survival models of mortality and hospitalizations, adding them to the models had almost no impact on the estimated vaccination effect (Table 2). This could be partly because health care use and indicators of comorbidities (e.g., diagnoses) tend to correlate in claims datasets [34], and thus health care use might not add substantial explanatory information once the indicators of comorbidities are already in the model.

Vaccination is usually associated with decreased risk for hospitalization [35]. The seemingly paradoxical increase observed in our study could be due several reasons. First, it could reflect that vaccinated patients had a higher risk of becoming infected (e.g., exposure in public spaces, work, or family) or suffer complications requiring hospitalization (e.g. impaired immune system), which was not captured by the available variables. Second, SwissDRG codes used to define influenza-related hospitalizations might not be specific enough. Some hospitalizations could have been related to other infections instead – which would not be influenced by the vaccination, but could be higher in the vaccinated group due to comorbidities or other risk factors. Third, some hospitalizations could be driven by patient or physician preferences, although we deem this unlikely, as the selected SwissDRG codes reflect serious medical conditions rather than elective treatments.

Although more hospitalizations were observed among vaccinated persons in our study, mortality afterward was lower. This hints at a potential attenuating effect of influenza vaccination.

We did not find studies directly reporting such effect for vaccination. However, some indirect observations suggest possible explanations. In a population-level study of specific hospitalizations and subsequent mortality in Norway, Ruiz et al. [36] observed higher influenza hospitalization rates but lower subsequent mortality for patients with type 2 diabetes compared to non-diabetic patients (although vaccination was associated with less frequent hospitalization in both groups). Potentially, type 2 diabetes in the Ruiz et al. study – and comorbidities not fully controlled for in vaccinated persons in our study – lead to lower hospital admission thresholds and thus apparent increase in hospitalizations but not worse subsequent mortality.

Decreased mortality and other severe outcomes, such as the need for intensive care treatment, in vaccinated patients after influenza-related hospitalizations have been observed in a variety of age and patient groups [3,37–39], although not consistently so [40,41]. Our study was different from most of those referenced because we considered deaths not only immediately after hospitalization, but during the whole influenza season (or after season period). While the observed effect size was not statistically significant in our study (Table 3), this may be due to a small number of events.

Our study was also different from those mentioned in that we used a multi-state model for mortality and hospitalizations, thereby considering the competing risks of these events. Competing risks pose a problem when any other outcome than mortality is analyzed, particularly in older populations with high morbidity. We found only one comparable study that considered death as a competing risk for intensive care unit (ICU) admission and hospital length of stay [3]. However, we did not find studies analyzing death as a competing risk for influenza-related hospitalization. While planning this study, we expected that the competing risk of death could result in seemingly paradoxically increased hospitalization risk in the vaccinated population. Although the

paradoxical effect persisted, its size was slightly smaller (closer to null effect) in the multi-state model (compare [Tables 2 and 3](#)).

In this study, we did not model the before season effect of vaccination. Although null effect of vaccination before season is argued to be essential as a check for residual confounding and the validity of an observational study [9], this condition could probably only be fulfilled in a randomized trial. Many observational studies comparing the effect of vaccination before, during and after influenza season have found that the before season effect is the highest, while the after season effect is often smaller than during the influenza season [18]. Ultimately, different populations are compared in these periods, as deceased persons do not enter subsequent periods of analysis. Although using after season instead of before season estimates does not avoid this issue, analyzed patients in these periods at least have the same temporal window to receive vaccination and be exposed to influenza.

Observational cohort studies based on secondary administrative data have been criticized in influenza effectiveness research as not suitable for eliminating confounding and bias. We aimed to improve the validity of our study by systematically and iteratively reviewing its design and focusing research question in an effort to minimize bias. Explicit consideration of all the elements of the PICO could be used to improve other observational studies of influenza vaccination and beyond. The approach draws attention to the selection of specific outcomes and to the comparability of groups – a strategy similar, but not as explicit and structured as specifying an emulated target trial [42]. In contrast, PICO approach is not an independent study design strategy and does not provide guarantees (e.g., of eliminating all confounding). Instead, it provides guidance for defining the research question that would be meaningful and feasible to answer with a given data source.

4.1. Limitations

This study has several limitations. First, we cannot entirely rule out residual confounding, given the use of secondary administrative data. We controlled for PCG-assessed comorbidity, health care use, and expenditure; however, these are imperfect proxies of individuals' health status [34]. Further confounders such as pneumococcal vaccination and the severity of measured comorbidities could not be controlled for. Second, misclassification could be present due to vaccination paid out-of-pocket. Vaccination provided before the deductible is exceeded is not reimbursed; in case the invoice is not automatically submitted to the health insurance, it is not recorded in the claims-based dataset. However, we included only people with chronic diseases, who are likely to exceed their deductible, especially by the time window of vaccination (September–December). Also, vaccination coverage in our study, particularly in older persons, did not differ substantially from that reported by other sources. Third, our dataset lacked outpatient diagnostic and inpatient test information. Therefore, we could not use even more specific outcomes, such as laboratory-confirmed influenza infection. Fourth, as baseline covariates such as chronic conditions and health care use were recorded once (at the end of 2013), we could not adjust for time-varying confounding.

Finally, a general caveat of influenza vaccination effectiveness research is that the vaccine and prevalent virus match changes every year. In 2014/2015, it was rather low [26]. The comparability of results from different seasons is debatable. However, the primary aim of this study was not to precisely estimate the effect size of a particular vaccine/virus match but to see if an attenuating effect of vaccination could be gleaned from administrative claims data in general.

5. Conclusions

In this study, influenza vaccination was associated with more frequent specific hospitalizations, but decreased risk of mortality overall and after such hospitalization in patients with chronic diseases. Our approach of iteratively considering each PICO element helped to consider various sources of bias in the study sequentially. The selection of appropriate, specific outcomes makes the link between intervention and outcome more plausible and can reduce the impact of confounding. Administrative data and cohort studies can be useful in influenza vaccine effectiveness research – if not for estimating precise effect sizes, then at least for uncovering potential mechanisms of the effect in different populations. Further studies with administrative data on vaccine effectiveness should carefully consider the selection of outcome, population, and confounding variables, in order to achieve the best possible study design.

Authorship contribution statement

MS, VvW and HD developed the underlying study program. AU and VvW designed the study, with significant contributions from MS, HD, OG and WW. BB, EB, CB did data preparation and management. AU and VvW performed statistical analysis and drafted the manuscript, with major contribution from MS. All authors together interpreted study results, critically revised the manuscript and approved for submission. All authors attest they meet the ICMJE criteria for authorship.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MS declares a grant from Helsana Insurance Group, outside the submitted work. Helsana Group provided support in the form of salaries for authors BB, EB and CB, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The other authors declare no competing interests.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2020.06.019>.

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